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Yellow fever revaccination guidelines change – a decision too feverish?

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On 17 May 2013, the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization announced a paradigm change regarding yellow fever (YF) vaccination policy, stating that there was no need for revaccination of immune-competent individuals 10 years after an initial vaccination [1]. Supplies of yellow fever vaccine are regularly overstretched. Reduction in the need for revaccination would increase the amount of vaccine available; therefore, the importance of this policy change should not be underestimated. However, there are important issues that render the basis for this bold move questionable.

The actual policy change hinges on information compiled in a comprehensive background paper [2] on long-term immunogenicity of the 17D YF vaccine. It includes a to date unpublished systematic review by Gotuzzo and colleagues postulating that evidence for lifelong immunity in healthy subjects was overwhelming (although the data referred to in support of this notion [2] showed that confidence in the estimate of the effect is limited). Further unpublished data were taken into account, confirming the risk of yellow fever vaccine-related viscerotropic disease following vaccination of elderly individuals, and recent research by Rafferty and colleagues into the role of cellular and innate immunity in the response to vaccination [E. Rafferty, unpublished data]. The revaccination policy was previously examined in 2003. It was stated at that time that the recommendations in International Health Regulations (IHR) since 1965 were based on limited evidence, which at that time was interpreted with caution, thus allowing for a safety margin of error [3]. To that end, the new recommendation announced on 17 May 2013 is remarkable because since 1965 few data on the duration of immunity have been published, and these provide only a limited base for this policy change.

As it stands, we question the conclusion that lifelong protection is sufficiently supported by the evidence presented in the background paper [2]. We identify the following remaining issues, which in our view ought to be considered.

- Currently, the presence of neutralizing antibodies against 17D-YFV is officially considered the best available proxy of protection after yellow fever vaccination. However, the use of different techniques and PRNT assay cut-off values to define protection hampers uniform interpretation of the study results (table 1 in reference [2]). With the PRNT, the capacity of a given dilution of immune serum to prevent plaque formation by 17D-YF virus in a cell culture in comparison to non-immune serum is expressed as percentage neutralization. In the cited studies, this percentage varies from 50% to 90% in serum dilutions ranging from 1:2 to >1:40. We strongly advocate the use of a universally accepted cut-off value (preferably expressed in international units using a reference serum) to define protection in future studies.
- The small number of documented cases of break-through infections might be an underestimate, as post-vaccination surveillance in most endemic areas is poor. With regard to outbreaks of yellow fever that occurred in Nigeria during the 1980s, it was found, in a limited survey, that almost all unvaccinated individuals aged 20 years and older had neutralizing antibodies. This implies that ongoing endemic transmission boosted the immunological memory in previously immunized individuals; however, there is the problem of flavivirus antibodies cross-reacting with flaviviruses other than the infective agent.
- The recommendation for revaccination predominantly applies to travellers. The lack of documented vaccine failures in travellers who have been vaccinated against yellow fever virus can be explained by the rarity of yellow fever in travellers in general and does not exclude the possibility of waning immunity.
- Some studies show long-term immunity, but not in all individuals. Percentages range from 70% to 96% (table 1 in reference [2]). So, after >20 years following vaccination, 4–30% of vaccinated individuals do not have neutralizing antibodies.

- We acknowledge that immune memory of yellow fever vaccine may persist even in the absence of neutralizing antibodies, but we doubt that (given the short incubation period) this will suffice to regularly protect all individuals against yellow fever virus infection.

We agree with the statement of the working group that many uncertainties remain. These knowledge gaps reduce confidence in the recommendation to immediately completely abolish revaccination. A more prudent approach would be to increase the revaccination interval from 10 to 20 years, and to define a cut-off percentage of the vaccine population that should be protected in order to define acceptable efficacy. At the same time, improved post-vaccination surveillance on a global scale should be implemented (although we acknowledge the practical difficulties), and studies to gain more insight into the presence of (cellular) immunity in those individuals not exhibiting neutralizing antibodies should be conducted. In practical terms, we advocate the use of unequivocal PRNT cut-off values to define protection expressed in international units by using a reference serum, and to define the lower level of seroprotection that is deemed acceptable in various populations that are at risk of contracting yellow fever.

In conclusion, SAGE favours a quantum leap in YF revaccination policy towards non-revaccination of healthy individuals, which stands in stark contrast to the remaining gaps in our knowledge. At the same time, they justifiably remain much more cautious about the safety of the vaccine and the duration of protection in selected populations with diminished immunity. We believe the best way forward at this moment is to moderately extend the revaccination interval from 10 to 20 years, whilst initiating global post-vaccination surveillance and fostering research into the kinetics and mechanisms of protection.

References

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